IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE HONORABLE BOARD OF PATENT APPEALS

In re Application of:	Group Art unit: 1631
David Farrow	Confirmation No. 7906
Serial No.: 10/601,378	Examiner: Karlheinz R. Skowronek
Filed: June 23, 2003	Attorney Docket: 93292-1
For: Nano and Micro-Technology Virus Detection Method and Device	PTO Customer No.: 22463

APPELLANT'S BRIEF UNDER 37 C.F.R. 41.37

The Assistant Commissioner of Patents
Washington, D.C. 20231
U.S.A.

Dear Sir or Madam:

The following is the Appellant's Brief, submitted under the provisions of 37 C.F.R. 41.37. The fee of $270 (small entity) required by 37 C.F.R. 41.20(b)(2) is enclosed.

Real Party in Interest

The real party in interest is the assignee of record, i.e. ACCELLA SCIENTIFIC INC., 330 Bay St., Suite 1100, Toronto, Ontario, Canada, M5H 2S8.

Related Appeals and Interferences

There are no related appeals or interferences that will directly affect, be directly affected by or have a bearing on the present appeal.

Status of Claims

The present appeal is directed to all of the pending claims in this application, namely, claims 1-5, 7, 8 and 22-29, all of which claims have been rejected.

Status of Amendments

No amendments have been filed after final rejection.

Summary of Claimed Subject Matter

The pending claims in the present application are directed to methods of detecting the presence of an analyte particle in a sample, using a combination of mechanical and biochemical steps in a particular order and in particular locations within the device to detect the physical presence or absence of residue within a chamber in the device. The presence or absence of the residue is used as an indicator or the presence of an analyte in an original fluid, without the need for complex chemical analysis.

Independent Claim 1

Independent claim 1 is directed to a method for detecting the presence of an analyte particle in a fluid, said method comprising, sequentially:

filtering a sample of said fluid (para. 8, lines 3-4; para. 10, lines 3-4) from a first chamber (e.g. first fluid chamber 14; para. 24, line 2; Fig. 1) to a second chamber (e.g. second fluid chamber 16; para. 24, line 2; para. 31, lines 1-2;

para. 41, lines 1-2; para. 42, lines 1-7; Fig. 1) through a filter (e.g. filter 18; para. 27, line 2; Fig. 1) sized to pass said analyte particle and particles smaller than said analyte particle (para. 31, lines 2-4; para. 42, lines 2-5), retaining in said first chamber particles in said sample larger than said analyte particle (para. 31, lines 4-5; para. 42, line 5; Fig. 2) thereby forming in said second chamber a filtered sample (para. 32, lines 1-2; para. 42, lines 6-7; Fig. 2);

adding to said filtered sample in said second chamber a reagent (e.g. CD4 glycoprotein particles 38; para. 32, lines 2-5 and 9-10; para. 42, lines 7-9; Fig. 3) that specifically interacts with said analyte particle (para. 8, lines 4-5; para. 10, lines 5-6; para. 32, lines 6-8 and 10-14; para. 42, lines 8-12) to form a reagent-analyte particle complex that is larger than said analyte particle (e.g. CD4-HIV complex 40; para. 8, lines 5-6; para. 10, lines 5-6; para. 32, lines 6-8 and 14-16; para. 34, lines 7-9; para. 42, lines 11-12; para. 43, lines 6-8; Fig. 3);

filtering said filtered sample (para. 8, lines 8-9; para. 34, lines 3-9; para. 43, lines 1-2; Fig. 4) from said second chamber through a filter sized to pass particles that are smaller than said reagent-analyte particle complex (e.g. filter 18, filter 18"; para. 10, lines 6-7; para. 34, lines 3-9; para. 43, lines 4-8; Figs. 4 and 5) thereby forming in said second chamber a further filtered sample (para. 34, lines 8-9; para. 36, line 1; para. 43, lines 7-8);

testing said further filtered sample in said second chamber for the presence of residual particles (para. 8, lines 9-11; para. 10, lines 7-9; para. 36, lines 1-11; para. 44, lines 1-6), wherein the presence of said residual particles identifies the presence of said reagent-analyte particle complex in said second chamber (para. 36, lines 6-11; para. 43, lines 1-4), and wherein the presence of said-analyte particle complex is indicative of the presence of said analyte particle in said fluid (para. 8, lines 9-11; para. 10, lines 7-9) and wherein the absence of said reagent-analyte particle complex in said second chamber is indicative of the absence of said analyte particle in said fluid (para. 37, lines 1-2; para. 44, lines 4-6).

Independent Claim 22

Independent claim 22 is also directed to a method to detect analyte particles in a sample; claim 22 is similar to independent claim 1, but specifies that the analyte to be detected is human immunodeficiency virus (e.g. HIV 36; para. 29, lines 7-9; Figs. 2-4). The mapping of the claim limitations to the specification set forth above for claim 1 is also applicable to claim 22.

Independent Claim 26

Independent claim 26 is also directed to a method to detect analyte particles in a sample in which the analyte particles are human immunodeficiency virus.

Specifically, the method claimed in claim 26 is directed to a method for detecting the presence of human immunodeficiency virus in a fluid, said method comprising:

filtering a sample of said fluid (e.g. blood sample 30 and first filter 18'; para. 8, lines 3-4; para. 10, lines 3-4; para. 42, lines 1-2; Fig. 5) to remove all particles in said sample larger than said human immunodeficiency virus (HIV 36; para. 31, lines 2-5; para. 42, lines 2-5; Fig. 2) to form a filtered fluid (para. 32, lines 1-2; para. 42, lines 6-7);

introducing said filtered fluid into a chamber (e.g. second fluid chamber 16'; para. 31, lines 1-2; para. 32, lines 1-2; para. 42, lines 5-12; para. 43, lines 1-2; Fig. 5);

adding to said filtered fluid a reagent that provides a specific binding site for any human immunodeficiency virus in said filtered fluid (e.g. CD4 glycoprotein particles 38; para. 8, lines 4-5; para. 10, lines 5-6; para. 32, lines 2-8 and 10-

14; para. 42, lines 7-12) to form a reagent-human immunodeficiency virus complex (e.g. CD4-HIV complex 40) that is larger than said human immunodeficiency virus in said chamber (e.g. chamber 17'; para. 8, lines 5-6; para. 10, lines 5-6; para. 32, lines 6-8; para. 34, lines 7-9; para. 42, lines 11-12; para. 43, lines 6-8; Figs. 3 and 5);

filtering said sample after said adding (e.g. filter 18, second filter 18"; para. 8, lines 8-9; para. 34, lines 3-9; para. 43, lines 1-2) to remove particles from said chamber that are smaller than said reagent-human immunodeficiency virus complex (para. 10, lines 6-7; para. 34, lines 3-9; para. 43, lines 4-8) to form a remaining sample in said chamber (para. 34, lines 8-9; para. 36, line 1; para. 43, lines 7-8);

testing said remaining sample in said chamber for the presence of a residue of said reagent-human immunodeficiency virus complex (para. 8, lines 9-11; para. 10, lines 7-9; para. 36, lines 1-11; para. 44, lines 1-6), wherein the presence of said residue in said chamber identifies the presence of said human immunodeficiency virus within said fluid (para. 8, lines 9-11; para. 10, lines 7-9; para. 36, lines 6-11; para. 43, lines 1-4) and wherein the absence of said residue in said chamber identifies the absence of said human immunodeficiency virus within said fluid (para. 37, lines 1-2; para. 44, lines 4-6).

Grounds of Rejection to be Reviewed on Appeal

The grounds of rejection to be reviewed on appeal are as follows:

A. Rejection of claims 1-5, 7, 8 and 22-29 under 35 U.S.C. 103 as obvious having regard to Tullis et al., *American Clinical Laboratory* (2001) Oct/Nov, 22-23 (hereinafter "Tullis"), in view of US 6,391,657 (hereinafter "Bernhardt"), in view of US 2002/0042125 (hereinafter

"Petersen"), in view of newly cited WO 01/85341 (hereinafter "Piesold"); and

B. Rejection of claims 1-5, 7, 8 and 22-29 under 35 U.S.C. 103 as obvious having regard to US 2004/0072278 (hereinafter "Chou"), in view of Bernhardt, in view of newly cited Piesold.

Argument

A. Rejection of claims 1-5, 7, 8 and 22-29 under 35 U.S.C. 103 as obvious having regard to Tullis, in view of Bernhardt, in view of Petersen, in view of Piesold.

Claims 1-5, 7, 8 and 22-29 remain rejected under 35 U.S.C. 103 as obvious in view of the four reference combination of Tullis, Bernhardt, Petersen and Piesold.

In order to reject a claim under 35 U.S.C. 103, the Examiner must establish a) that all claim limitations are found in the references; b) motivation in the references or in the art to modify the references or to combine the references to arrive at the claimed invention; and c) a likelihood of success.

Applicant respectfully submits that pending claims 1-5, 7, 8 and 22-29 are not obvious having regard to the combination of cited references Tullis, Bernhardt, Petersen and Piesold, for at least the following reasons.

i. Claims 1-5, 7 and 8

Applicant submits that review of Tullis, Bernhardt and Petersen together in view of Piesold reveals that the new four reference combination does not disclose, describe or suggest testing for the presence of residual particles to identify the presence of a reagent-analyte particle complex within a chamber in which the

reagent-analyte complex is formed, as claimed in currently pending independent claim 1. The Examiner has thus failed to establish a *prima facie* case of obviousness.

For convenience, independent claim 1 as currently pending is set out below.

Claim 1: (previously presented) A method for detecting the presence of an analyte particle in a fluid, said method comprising, sequentially:

filtering a sample of said fluid from a first chamber to a second chamber through a filter sized to pass said analyte particle and particles smaller than said analyte particle, retaining in said first chamber particles in said sample larger than said analyte particle thereby forming in said second chamber a filtered sample;

adding to said filtered sample in said second chamber a reagent that specifically interacts with said analyte particle to form a reagent-analyte particle complex that is larger than said analyte particle;

filtering said filtered sample from said second chamber through a filter sized to pass particles that are smaller than said reagent-analyte particle complex thereby forming in said second chamber a further filtered sample;

testing said further filtered sample in said second chamber for the presence of residual particles, wherein the presence of said residual particles identifies the presence of said reagent-analyte particle complex in said second chamber, and wherein the presence of said-analyte particle complex is indicative of the presence of said analyte particle in said fluid and wherein the absence of said reagent-analyte particle complex in said second chamber is indicative of the absence of said analyte particle in said fluid.

Thus, in pending claim 1, a combination of steps is used to sequentially filter a sample to retain particles larger than the analyte in a first chamber, and pass the filtered sample to a second chamber. In the second chamber the apparent size of the analyte may be enlarged by adding a reagent to form a reagent-analyte particle complex, for easy detection. The reagent-analyte particle complex may be isolated in the second chamber by filtering to remove particles smaller than the complex. Residual particles may be tested for in the second chamber. Presence/absence of the residual particles in the second chamber is

indicative of the presence/absence of the analyte particle in the initial fluid sample. This combination and sequence of steps is not disclosed, described or suggested by the combination of Tullis, Bernhardt, Petersen and Piesold, and a skilled person would not be motivated to combine these references to arrive at the subject matter of claim 1. Particularly, none of the cited references provide the step of testing for the presence of residual particles within the chamber in which a reagent-analyte particle complex is formed.

Tullis describes an "HIV Hemopurifier" - a purification filter for removing HIV particles from infected blood samples. Specifically, the device in Tullis is a standard, hollow-fiber affinity hemodialysis cartridge used to filter HIV particles away from larger blood cells and then capture the HIV particles using immobilized antibodies. The hollow fibers each have multiple submicron-sized pores to allow passage of the virus, while preventing the passage of larger preformed blood elements, through the pores into an extra-fiber space surrounding the hollow fibers. The extra-fiber space includes antiviral antibodies covalently coupled to a solid support. Any particles smaller than the submicron pores will flow into the extra-fiber space and any HIV particle that passes into the extra-fiber space will be bound by the immobilized antibody already present in the extra-fiber space. Unbound particles (e.g. non-HIV particles), regardless of size, can then freely move back through the same submicron pores, thus passing from the extra-fiber space back into the hollow fiber and eventually flowing out of the hollow fiber and out of the device.

Tullis thus discloses a device that relies only a single filtration step. Tullis simply fails to disclose a subsequent filtering step as claimed. The filter in Tullis is used primarily to prevent larger preformed blood elements (such as cells) from flowing into the extra-fiber space (see page 22, the sentence bridging columns 1 and 2). The pores are sized to permit smaller particles, such as any HIV that might be present, to flow into the extra-fiber space and thus contact the immobilized antibody. Given that any formed antibody-HIV complex would automatically be

trapped in the extra-fiber space due to the fact that the antibody is immobilized by covalent coupling to the solid support, no second filtering step is required in Tullis.

Furthermore, since the antibody in Tullis is immobilized, the pore size in the Tullis device does not need to be selected in order to trap any residue of an antibody-HIV complex that is formed—such a complex will automatically be trapped within the extra-fiber space by virtue of the covalent coupling of the antibody to the solid support. Indeed, there is also no disclosure, description or suggestion in Tullis that the pore size should be selected to retain a reagent-analyte complex while allowing smaller particles to flow out of a chamber in which any reagent-analyte complex is formed.

Thus, Tullis does not disclose, describe or suggest any second filtering to retain a residue of a reagent-analyte complex within a chamber in which it is formed, nor use of a filter sized to pass particles that are smaller than the reagent-analyte particle complex thereby forming in a second chamber a further filtered sample, in contrast to current claim 1.

As well, Tullis does not disclose, describe or suggest testing for the presence of residual particles in the second chamber in order to identify the presence of the analyte in the original fluid, as claimed in claim 1. In claim 1, after the second filtering step, the presence (or absence) of residual particles in the chamber in which the reagent-analyte particle is formed is indicative of the presence (or absence) of the analyte in the original fluid. However, in Tullis, the antibody is immobilized within the extra-fiber space, and mere testing will always reveal the presence of some sort of residue: either antibody or antibody-HIV complex, if formed. Thus, there is no way to use the device of Tullis to identify the presence or absence of HIV in the original fluid based on the presence or absence of residue. Testing for residue in the device in Tullis would always provide a positive result, regardless of the presence of HIV in the original sample or not.

Applicant submits that the device in Tullis is simply not designed to test for the presence of formed residue within the extra-fiber space, and that Tullis in fact teaches away from detecting the presence or absence of residue within a chamber in the device in which a reagent-analyte complex is formed.

Specifically, Tullis indicates, at page 23, column 1, paragraph 3, that PCR analysis was performed on RNA extracted from virus trapped in the device in order to confirm the effectiveness of the device.

First, as stated above, even if the extra-fiber space is considered analogous to the second chamber, the mere presence of residue within the extra-fiber space of the Tullis device is not sufficient to indicate that presence of HIV in the original sample. Rather, as Tullis indicates, the residue itself must be extracted and further analyzed in order to confirm the presence of the virus within the residue. Extraction of viral RNA followed by PCR amplification as described in Tullis is used to further analyze the content of any residue from the extra-fiber space; the PCR reaction detects the presence of the virus only, since the antibody will not contain any RNA and cannot be detected by nucleic acid polymerase chain reaction amplification methods. Thus, using the device and method in Tullis, the mere presence of residue is not sufficient and any testing described in Tullis is actually further testing of the content of the residue, rather than testing for the presence of residue.

Second, the PCR detection in Tullis was not performed within the chamber in which the reagent-analyte particle complex is formed, but was performed in a separate PCR thermocycler. Thus, Applicant points out that testing was required to be performed on samples extracted from the device, rather within the device itself, since the device in Tullis is not designed to identify the presence of HIV particles based on the presence of residual particles within a chamber of the device.

Third, Applicant submits that subsequent testing for an isolated analyte molecule by PCR, in the absence of the previous filtering steps of the present claims and removed from the formed reagent-analyte molecule formed within the device used to filter the sample (in fact, removed entirely from the device itself), is no different than testing for the analyte directly in a sample using RNA extraction and PCR methods without first conducting the filtering and affinity complexing of the present method. In doing so, the advantages provided by the presently claimed methods, including the ease, efficiency, speed and ability to test a small sample volume, are lost, and a sample may as well be subjected to known analysis methods involving RNA extraction and subsequent PCR analysis in order to detect the presence of a virus analyte particle.

Fourth, the testing described in Tullis was performed in order to confirm the effectiveness of the device, rather than confirm the presence or absence of HIV in the original sample. Given that the device described in Tullis is designed for decontamination and not detection, and given that Tullis describes using external PCR testing for confirmation of the presence of HIV trapped within the device, Applicant submits that the subsequent testing described in Tullis for quality control purposes is in no way analogous to the testing as claimed in claim 1.

Accordingly, Applicant submits that the extraction and testing described in Tullis does not constitute testing a further filtered (i.e. twice filtered) sample for the presence of a residue within the second chamber to assess the presence/absence of the analyte in the original fluid, contrary to present claim 1. At most Tullis describes testing for the presence of the analyte particle itself by removal of the virus (analyte particle) from the filtering device entirely, with subsequent direct detection of the virus (analyte particle) alone in a separate device. Thus, Applicant submits that Tullis does not disclose, describe or suggest testing for the presence of residual particles within a chamber in which a reagent-analyte particle complex is formed, as is required in independent claim 1 of the present application.

Based on the foregoing, Applicant submits that the Tullis reference would not render the subject matter of present claim 1 as obvious and would not motivate a skilled person to arrive at the method of present claim 1.

Tullis was cited in combination with the Bernhardt reference. Applicant submits that Bernhardt does not compensate for the deficiency of the Tullis reference and does not combine with Tullis to render present claim 1 as obvious. In particular, Bernhardt does not compensate for the deficiencies of Tullis, as the Bernhardt reference does not disclose, describe or suggest testing for the presence of residual particles within the chamber in which a reagent-analyte particle complex is formed, as is required by pending claim 1.

Instead, Bernhardt relates to a method for removing viral particles from an aqueous protein solution, and is mostly concerned with providing a resultant decontaminated protein solution free from virus.

Examples 1 and 2 of Bernhardt (columns 3 and 4) describe testing the filtrate after filtration (and not the residue/retentate, which is the sample retained as the further filtered sample in present claim 1). The filtrate in Bernhardt would contain particles smaller than any reagent-analyte particle complex, but would not contain any reagent-analyte particle complex itself. Thus, in Bernhardt there is no testing for the presence of residual particles in a chamber in which a reagent-analyte particle complex is formed, as required in current claim 1. The approach described in Bernhardt involves the additional steps of collecting filtrate and then testing for the analyte directly in the filtrate once collected. This is due to the fact that in Bernhardt the original fluid was known to contain analyte particles and the described method is concerned with providing a decontaminated filtrate, and thus the testing is designed to look for the presence or absence of analyte particle in the final filtrate to determine the effectiveness of decontamination.

Thus, Bernhardt does not compensate for the defect in Tullis. Tullis and Bernhardt do not combine to render claim 1 obvious, since neither reference

nor the combination of references provides the necessary sequence and combination of various steps of filtration, specific interaction between a reagent and analyte particle and testing for the presence of residual particles within the chamber in which a reagent-analyte complex is formed as claimed in present claim 1. Neither does the combination of Tullis and Bernhardt suggest or motivate a skilled person to arrive at the method of claim 1.

However, Tullis and Bernhardt were cited in combination with Petersen. Petersen is merely cited for its disclosure of an injection molded plastic filter device (which feature is not found in present claim 1) and does not compensate for the above-described deficiencies of Tullis and Bernhardt. Petersen does not disclose, describe or suggest testing for the presence of residual particles within a chamber in which a reagent-analyte particle complex is formed.

Presently, Tullis, Bernhardt and Petersen are cited in combination with Piesold. In the final office action dated May 21, 2008, the Examiner withdrew the rejection based on the combination of the three references Tullis, Bernhardt and Petersen, as he was persuaded by amendments and arguments made in Applicant's response filed February 15, 2008, that this combination of references does not render the present claims obvious. Thus, the Examiner has taken the position that the current claims are not obvious in view of the combination of Tullis, Bernhardt and Petersen, and that the inclusion of the newly cited Piesold reference into the combination of references provides the missing components not supplied by Tullis, Bernhardt and Petersen together in order to render the claims obvious.

Applicant submits that Piesold does not compensate for the deficiencies of the combination of Tullis, Bernhardt and Petersen and thus the combination of the four cited references does not render present claim 1 obvious.

Piesold does not disclose, describe or suggest filtering out particles larger than an analyte particle or formation of a reagent-analyte complex within a chamber. Piesold also does not disclose, describe or suggest testing for residual

particles within the chamber in which the complex is formed, which element is also not supplied by the combination of Tullis, Bernhardt and Petersen.

Rather, Piesold merely describes a conventional flow filter device and method that uses a standard a single filtration step to trap particles of a pre-determined size (analyte) by allowing other species smaller than the desired particle to flow through the filter, thus providing a device for performing flow-through reactions. As can be seen from Figure 2 and page 7 of Piesold, the device in Piesold has a central reaction chamber 10 formed by the placement of a filter 4 around the inlet 2, through which sample, reaction solution and wash solutions are flowed. The filter 4 defines the reaction chamber 10 and separates the reaction chamber 10 from a surrounding waste chamber 18. The filter is positioned so as to trap the particles 6 of pre-determined size (analyte) within the central reaction chamber 10 while allowing flow of the various solutions from the inlet 2, through the reaction chamber 10 past the trapped particles 6, to surrounding waste chamber 18 and then to the outlet 16 of the device. Thus, the device in Piesold is designed to trap an analyte particle within a first chamber while allowing particles smaller than the analyte to flow through the filter. This is in contrast to the requirement of the present claim 1, which requires a first filtering step in which particles larger than the analyte are trapped by a filter and the analyte particles and smaller particles flow through the filter into a second chamber.

Even if the first filtration step of Piesold could be understood to be a first filtration step that traps particles larger than an analyte particle (which Applicant submits is not correct), such an interpretation would mean that the analyte particle of interest in fact flows through the filter 4 into the surrounding waste chamber 18. There is no subsequent step that would result in a reagent added to the waste chamber 18 to specifically bind to an analyte particle within the waste chamber with a resulting formation of a reagent-analyte particle complex as required in present claim 1. Similarly, Piesold does not describe a second filtration step to trap a reagent-analyte particle within the waste chamber 18 while allowing smaller particles to flow through a filter, or testing for the presence of residual particles

within the waste chamber, as required by present claim 1. In fact, there is no indication in Piesold that once a particle has entered into waste chamber 18 there is any mechanism to retain the particle within waste chamber 18 and to prevent the particle from flowing to outlet 16.

The Examiner describes the device in Piesold as having a waste chamber that is a first chamber and reaction chamber that is a second chamber. However, Applicant points out that the direction of solution flow in Piesold is from the inlet 2, through the reaction chamber 10, then through the waste chamber 18 and on through to the outlet 16. Thus, the Examiner's description is in fact the reverse of that described in Piesold.

In addition, the Examiner defined the particle beads 6 used in Piesold as the reagent added to the reaction chamber 10. However, as clearly indicated in Piesold, the beads are the particles of interest that are added to the device and which are trapped in the reaction chamber 10. The filter 4 in Piesold holds the beads 6 (or the analyte particle of interest) in place while allowing solutions and smaller particles to flow through the filter 4 and eventually out of the device. In Piesold, the beads 6 are first prepared with a streptavidin-immobilized DNA strand and hybridized primer prior to addition to the device (page 13, lines 8-20). If the beads are to serve as the reagent particle, there is no analyte particle that has been previously filtered into the reaction chamber 10 away from particles larger than the analyte particle, as required by the present claim 1.

The monitoring device referred to by Examiner does not detect the presence of any residual particles, but rather is described as means of monitoring or detecting products of a chemical or biochemical reaction that occurs within the reaction chamber. In the example described on page 13 of the Piesold reference, light produced from a primer extension reaction is detected using a CCD camera. This does not equate to, or even suggest, testing for the presence of residual particles within the chamber in which a reagent-analyte particle complex is formed.

Applicant submits that the Examiner's interpretation of Piesold is not consistent with the description of Piesold. In order to relate Piesold to the invention as claimed in present claim 1 as the Examiner has done would require modification of the device in Piesold in such a manner as to destroy the purpose or function of the Piesold device, i.e. to reverse the flow backwards through the device in Piesold, destroying the function of filter 4 for trapping particle beads 6 within reaction chamber 10 (since there would be nothing stopping the beads from flowing out inlet 2). There is no reason to modify Piesold and there is no indication in Piesold, or indeed in any of the cited references, that the device in Piesold should in fact be modified or that there is any need to improve the device in Piesold, given the description in Piesold of a monitoring device with a reaction chamber that traps the particles of interest for the purpose of observing a chemical or biochemical reaction during flow-through reactions. Applicant submits that the Examiner's citation of the Piesold reference therefore does not support a *prima facie* case of obviousness.

Thus, for these reasons, Applicant submits that the Piesold reference does not compensate for the deficiencies of the combined Tullis, Bernhardt and Petersen references. The four references in combination do not disclose, describe or suggest testing for the presence of a residual particles within a chamber of the device in which a reagent-analyte particle complex is formed. Thus, the four references in combination cannot disclose, describe or suggest a method involving the sequential steps of

(1) filtering a sample of the fluid from a first chamber to a second chamber through a filter sized to pass the analyte particle and particles smaller than the analyte particle, retaining in the first chamber particles in the sample larger than the analyte particle thereby forming in the second chamber a filtered sample;
(2) adding to the filtered sample in the second chamber a reagent that specifically interacts with the analyte particle to form a reagent-analyte particle complex that is larger than the analyte particle;

(3) filtering the filtered sample from the second chamber through a filter sized to pass particles that are smaller than the reagent-analyte particle complex thereby forming in the second chamber a further filtered sample; and

(4) testing the further filtered sample in the second chamber for the presence of residual particles, wherein the presence of the residual particles identifies the presence of the reagent-analyte particle complex in the second chamber, and wherein the presence of the-analyte particle complex is indicative of the presence of the analyte particle in the fluid and wherein the absence of the reagent-analyte particle complex in the second chamber is indicative of the absence of the analyte particle in the fluid.

In addition, there is no reason that a skilled person would be motivated to combine Tullis, Bernhardt, Petersen and Piesold to arrive at the present method of claim 1. Tullis and Bernhardt are directed to devices and methods for purifying or cleaning biological samples. Piesold is directed to a device for sequestering particles while performing flow-through reactions in front of a monitoring device. Petersen is cited solely for the use of injection molded plastic. Applicant submits that there is no reason or motivation to combine such references having different purposes and that a skilled person in possession of these references would not arrive at a method for detecting the presence of an analyte particle in a fluid that involves the above sequential steps, as specified in present claim 1.

The Examiner states that Bernhardt shows that the described method will increase the safety of plasma proteins produced from human plasma and will allow for an increased rate of filtration (page 5, third paragraph of final rejection dated May 21, 2008). The Examiner also stated that Piesold suggests the described device may be used to implement multi-step reactions at a single location and that the device enhances the feasibility of miniaturizing assays.

Applicant submits that such suggestions and statements would not provide motivation to arrive at the specific sequence and combination of steps of filtration, specific interaction with a reagent and testing for a reagent-analyte particle

complex within the chamber in which the complex is formed, as set out in present claim 1. Neither of the Examiner's asserted reasons provide motivation to combine purification methods with a method for monitoring flow-through reactions, to modify the method for monitoring flow-through reactions in such a way that is contrary to and which destroys the purpose of the monitoring method, to arrive at the method of detecting an analyte in a fluid of present claim 1, which involves additional steps and sequences of steps not contained within the four cited references. The reasons provided by the Examiner relate to the method of the particular reference that provides the reason, but do not provide incentive to alter a purification method and a monitoring method to arrive at an entirely different method for detecting an analyte in a fluid.

Thus, Applicant submits that the references cited by the Examiner, in combination, do not provide all of the claim elements. In particular, none of the cited references discloses, describes or suggests testing for the presence of residual particles within a chamber in which a reagent-analyte particle complex is formed. Applicant also submits that there is no motivation to combine the cited references, without prior knowledge of the presently claimed invention, to arrive at a method as described in present claim 1.

Furthermore, given the lack of all of the claim elements and the lack of motivation to combine decontamination methods with a flow-through reaction monitoring method, Applicant submits that a skilled person could not have a reasonable expectation of success of the presently claimed analyte detection method, based on the combination of cited references. Thus, no *prima facie* case of obviousness has been made out based on the combination of Tullis, Bernhardt, Petersen and Piesold.

Claims 2-5, 7 and 8 are dependent, either directly or indirectly, on claim 1, and thus include all of the features as described above for claim 1. Thus, the above arguments presented for claim 1 also apply to claims 2-5, 7 and 8 and the

combination of the four cited references does not render claims 1-5, 7 and 8 obvious.

In view of the foregoing, reversal of the rejection of independent claim 1 and claims 2-5, 7 and 8 dependent thereon under 35 U.S.C. 103 in view of Tullis, Bernhardt, Petersen and Piesold, is therefore requested.

ii. Claims 22 to 25

Independent claim 22 includes the features and limitations of independent claim 1, but further specifies that the analyte particle is human immunodeficiency virus.

Based on the above arguments, Applicant submits that the four cited references in combination do not provide all of the claim elements of present independent claim 22. In particular, there is no disclosure, description or suggestion of testing for residual particles within a chamber in which a reagent-analyte particle is formed, which feature is also found in present claim 22.

Even though Tullis and Bernhardt both relate to cleaning human immunodeficiency virus particles from blood, provision of the feature of human immunodeficiency virus does not overcome the above described deficiencies of the combination of Tullis, Bernhardt, Petersen and Piesold.

Thus, as stated above, the combination of the four cited references does not provide all of the claim elements. As well, there is no reason or motivation to combine and modify the four cited references in order to arrive at a detection method for detecting the presence of human immundodeficiency virus in a sample as claimed in present claim 22. In light of the lack of all of the claim elements and motivation, a skilled person could not have any reasonable expectation of success, since there would be no reason to arrive at the method of claim 22. Furthermore, as stated above, the necessary modification required to adapt Piesold to the

present methods would destroy the intent, purpose and function of the device in Piesold and thus this reference does not support a *prima facie* case of obviousness.

Dependent claims 23 to 25 depend directly or indirectly from claim 22 and thus include all of the features of independent claim 22. For the same reasons as stated above for claim 1, Applicant submits that the combination of Tullis, Bernhardt, Petersen and Piesold references do not render claims 22 to 25 obvious.

In view of the foregoing, reversal of the rejection of independent claim 22 and claims 23 to 25 dependent thereon under 35 U.S.C. 103 in view of Tullis, Bernhardt, Petersen and Piesold, is therefore requested.

iii. Claims 26 to 29

Present independent claim 26 includes the features found in independent claims 1 and 22 of filtering a sample to remove particles larger than the analyte particle, specifically interacting a reagent with the analyte particle to form a reagent-analyte particle complex within a chamber, filtering to remove particles smaller than the reagent-analyte particle complex, and testing for the presence of residual particles. Claim 26 also specifies that the analyte particle is human immunodeficiency virus.

Thus, present independent claim 26 also includes the feature of testing for the presence of a residue within the chamber in which a reagent-human immunodeficiency virus (analyte) complex is formed. For the reasons stated above, the combination of Tullis, Bernhardt, Petersen and Piesold do not disclose, describe or suggest this feature.

Accordingly, Applicant submits that, as stated above for independent claims 1 and 22, the combination of the four cited references does not provide all of the claim elements; there is no reason or motivation to combine and modify the four

cited references in order to arrive at a detection method for detecting the presence of human immundodeficiency virus in a sample as claimed in present claim 26; and in light of the lack of all of the claim elements and motivation, a skilled person could not have any reasonable expectation of success, since there would be no reason to arrive at the method of claim 26.

Also as stated above, the necessary modification required to adapt Piesold to the present methods would destroy the intent, purpose and function of the device in Piesold and thus this reference does not properly support a *prima facie* case of obviousness.

Dependent claims 27 to 29 depend directly or indirectly from independent claim 26 and thus include all of the features of claim 26. Thus, for the same reasons as stated above for claim 1, Applicant submits that the combination of Tullis, Bernhardt, Petersen and Piesold references do not render claims 26 to 29 obvious.

In view of the foregoing, reversal of the rejection of independent claim 26 and claims 27-29 dependent thereon under 35 U.S.C. 103 in view of Tullis, Bernhardt, Petersen and Piesold, is therefore requested.

B. Rejection of claims 1-5, 7, 8 and 22-29 under 35 U.S.C. 103 as obvious having regard to Chou, in view of Bernhardt, in view of Piesold.

Claims 1-5, 7, 8 and 22-29 remain rejected under 35 U.S.C. 103 as obvious in view of the combination of Chou, Bernhardt and Piesold.

Applicant respectfully submits that pending claims 1-5, 7, 8 and 22-29 are not obvious having regard to the combination of the Chou, Bernhardt and Piesold references, for at least the following reasons.

i. Claims 1-5, 7 and 8

Applicant submits that review of Chou and Bernhardt together in view of Piesold reveals that the new three-reference combination does not disclose, describe or suggest testing for the presence of residual particles within the chamber in which a reagent-analyte particle complex is formed, as claimed in currently pending claim 1. The Examiner has thus failed to establish a *prima facie* case of obviousness.

As stated above, in contrast to the present claims, Bernhardt does not disclose, describe or suggest testing for the physical presence of residual particles within the chamber in which a reagent-analyte particle complex is formed, the presence of which is indicative of the presence of the analyte particle in the original fluid sample.

Applicant submits that the Chou reference does not compensate for this defect in Bernhardt.

The Chou reference relates to microfluidics particle-analysis systems for manipulation and analysis of particles, and describes a number of different features that may be included within a microfluidics device. Chou does indicate that larger particles can be separated from smaller particles using filtration steps. Chou does also indicate that once a particle has been retained in the described microfluidics device such a particle can be analyzed by exposing the particles to desired reagents.

However, Chou does not disclose, describe or suggest contacting an analyte particle with a reagent molecule that specifically binds the analyte particle to form a complex prior to further size filtration steps. Chou also does not disclose, describe or suggest testing for the physical presence of residue within the chamber in which the complex is formed, as required by present claim 1. Chou does not suggest combining filtration and binding steps in the specific order and

combination as required in the detection method of present claim 1, and does not suggest at all that testing for the mere presence of a residue can be used as an indicator of the presence of an analyte in an original fluid, in contrast to present claim 1.

The Examiner states that Chou describes a microfluidics device with cascaded size selective combs. Applicant submits that a cascade of combs for filtering objects of different sizes at different stages would result in separation of sequentially smaller and smaller particles at each step in the cascade. Such a filtering arrangement does not suggest or provide an intervening step that involves making the apparent size of the analyte larger based on a specific interaction following a first filtration step, a subsequent second filtration step and then testing for the presence of residue remaining within the chamber in which a reagent-analyte complex is formed, as required by present claim 1.

The Examiner states that Chou states that particles may be treated with reagents and that reagent-particle complexes may be detected, citing paragraph 661 of the reference. This portion of the reference appears to be describing standard detection methods by treating with reagents in order to detect suitable characteristics of retained particles in order to identify the type or state of the particle. There is no reference or suggestion that mere presence of a residue can be used as an indicator of the presence of an analyte particle. The portion of the reference cited by the Examiner, and in fact the entire reference, does not mention testing for the mere presence (or absence) of residue remaining within the chamber in which a reagent-analyte particle complex is formed subsequent to filtering out particles smaller than the reagent-analyte particle complex, can be used as an indicator of the presence (or absence) of an analyte particle in an orginal fluid.

For at least these reasons, Applicant submits that the Chou reference cannot combine with the Bernhardt reference to compensate for the deficiencies of Bernhardt.

In the previous non-final office action dated August 15, 2007, the Examiner rejected the claims *inter alia* as obvious having regard to the combination of Chou and Bernhardt. These rejections were withdrawn in the final office action dated May 21, 2008, in light of amendments and arguments made in Applicant's response filed February 15, 2008. Thus, the Examiner has taken the position that the current claims are not obvious in view of the combination of Chou and Bernhardt, and that the inclusion of the newly cited Piesold reference into the combination of references provides the missing components not supplied by Chou and Bernhardt together in order to render the claims obvious.

As stated above, Piesold does not mention addition of reagent, formation of a reagent-analyte complex, filtration of particles smaller than the complex and testing for the presence of a residue within the chamber in which the complex is formed, as required by pending claim 1, and therefore does not compensate for the defect in Bernhardt together with Chou. Furthermore, as argued above, Applicant submits that citation of Piesold is not appropriate, since in order to relate Piesold to the invention as claimed in present claim 1 would require modification of the device in Piesold in such a manner as to destroy the intent, purpose or function of the Piesold device.

Thus, for these reasons, Applicant submits that the Piesold reference does not overcome the deficiencies of the combined Chou and Bernhardt references. None of the references supplies the element of testing for the physical presence of a residue within a chamber in which a reagent-analyte particle complex is formed, which presence is indicative of the presence of the analyte within an original fluid. As with the rejection set out in A. above, Applicant submits that the Chou, Bernhardt and Piesold references cited in combination in this rejection do not disclose, describe or suggest a method involving the sequential steps of

(1) filtering a sample of the fluid from a first chamber to a second chamber through a filter sized to pass the analyte particle and particles smaller than

the analyte particle, retaining in the first chamber particles in the sample larger than the analyte particle thereby forming in the second chamber a filtered sample;

(2) adding to the filtered sample in the second chamber a reagent that specifically interacts with the analyte particle to form a reagent-analyte particle complex that is larger than the analyte particle;

(3) filtering the filtered sample from the second chamber through a filter sized to pass particles that are smaller than the reagent-analyte particle complex thereby forming in the second chamber a further filtered sample; and

(4) testing the further filtered sample in the second chamber for the presence of residual particles, wherein the presence of the residual particles identifies the presence of the reagent-analyte particle complex in the second chamber, and wherein the presence of the-analyte particle complex is indicative of the presence of the analyte particle in the fluid and wherein the absence of the reagent-analyte particle complex in the second chamber is indicative of the absence of the analyte particle in the fluid.

Applicant further submits that a skilled person would not be motivated to combine Chou, Bernhardt and Piesold to arrive at the present method of claim 1.

Chou broadly describes microfluidic devices that can include size exclusion filters. Bernhardt is directed to a method for purifying or cleaning biological samples and Piesold is directed to a device for sequestering particles while performing flow-through reactions in front of a monitoring device. Applicant submits that a skilled person in possession of these references would not combine them and would not arrive at a method for detecting the presence of an analyte particle in a fluid that involves the above sequential steps.

The Examiner states that Bernhardt shows that the described method will increase the rate of filtration (page 11, first paragraph of final rejection dated May 21, 2008) and that the devices of Chou provide for improved speed, accuracy, safety and cost. The Examiner also stated that Piesold suggests the described

device may be used to implement multi-step reactions at a single location and that the device enhances the feasibility of miniaturizing assays. Applicant submits that such suggestions and statements would not provide motivation to arrive at the specific sequence and combination of filtration, specific interaction and testing within the chamber in which the specific interaction occurs, as set out in present claim 1. There is no motivation provided to make necessary amendments to Chou, Bernhardt and Piesold, and to include the additional step of testing for the presence of residue within a chamber in which a reagent-analyte particle complex is formed (which step is not disclosed, described or suggested in any of the three cited references) to use as an indicator of the presence of analyte in an original fluid, in order to arrive at the detection method of present claim 1.

Thus, Applicant submits that the combination of Chou, Bernhardt and Piesold does not provide all of the claim elements. In particular, none of the cited references discloses, describes or suggests testing for the presence of residual particles within a chamber in which a reagent-analyte particle is formed. Applicant also submits that there is no motivation to combine the cited references, without prior knowledge of the presently claimed invention, to arrive at a method as described in present claim 1.

Furthermore, given the lack of all of the claim elements and the lack of motivation to combine decontamination methods with a flow-through reaction monitoring method, Applicant submits that a skilled person could not have a reasonable expectation of success of the presently claimed analyte detection method, based on the combination of cited references. Thus, no *prima facie* case of obviousness has been made out based on the combination of Chou, Bernhardt and Piesold.

As stated above, claims 2-5, 7 and 8 depend directly or indirectly from claim 1 and thus for the above reasons, the combination of these three cited references does not render claims 1-5, 7 and 8 obvious.

In view of the foregoing, reversal of the rejection of independent claim 1 and claims 2-5, 7 and 8 dependent thereon under 35 U.S.C. 103 in view of Chou, Bernhardt and Piesold is therefore requested.

ii. Claims 22 to 25

Independent claim 22 includes the features and limitations of independent claim 1, but further specifies that the analyte particle is human immunodeficiency virus.

Based on the above arguments, Applicant submits that the four cited references in combination do not provide all of the claim elements of present independent claim 22. In particular, there is no disclosure, description or suggestion of testing for residual particles within a chamber in which a reagent-analyte particle is formed, which feature is also found in present claim 22.

Even though Bernhardt relates to cleaning human immunodeficiency virus particles from blood, provision of the feature of human immunodeficiency virus does not overcome the above described deficiencies of the combination of Chou, Bernhardt and Piesold.

Thus, as stated above, the combination of cited references Chou, Bernhardt and Piesold does not provide all of the claim elements. As well, there is no reason or motivation to combine and modify the cited references in order to arrive at a detection method for detecting the presence of human immundodeficiency virus in a fluid as claimed in present claim 22. In light of the lack of all of the claim elements and motivation, a skilled person could not have any reasonable expectation of success, since there would be no reason to arrive at the method of claim 22. Furthermore, as stated above, the necessary modification required to adapt Piesold to the present methods would destroy the intent, purpose and function of the device in Piesold and thus this reference does not properly support a *prima facie* case of obviousness.

Dependent claims 23 to 25 depend directly or indirectly from claim 22 and thus include all of the features of independent claim 22. For the same reasons as stated above for claim 1, Applicant submits that the combination of the Chou, Bernhardt and Piesold references do not render claims 22 to 25 obvious.

In view of the foregoing, reversal of the rejection of independent claim 22 and claims 23 to 25 dependent thereon under 35 U.S.C. 103 in view of Chou, Bernhardt and Piesold is therefore requested.

iii. Claims 26 to 29

As stated above, present independent claim 26 includes the features found in independent claims 1 and 22 of filtering a sample to remove particles larger than the analyte particle, specifically interacting a reagent with the analyte particle to form a reagent-analyte particle complex within a chamber, filtering to remove particles smaller than the reagent-analyte particle complex, and testing for the presence of residual particles within the chamber in which the complex is formed. As in claim 22, claim 26 specifies that the analyte particle is human immunodeficiency virus.

Thus, present independent claim 26 also includes the feature of testing for the presence of a residue within the chamber in which the reagent-human immunodeficiency virus complex is formed. For the reasons stated above, the combination of Chou, Bernhardt and Piesold does not disclose, describe or suggest this feature.

Accordingly, Applicant submits that, as stated above for independent claims 1 and 22, the combination of cited references Chou, Bernhardt and Piesold does not provide all of the claim elements; there is no reason or motivation to combine and modify the four cited references in order to arrive at a detection method for detecting the presence of human immundodeficiency virus in a fluid as claimed in

present claim 26; and in light of the lack of all of the claim elements and motivation, a skilled person could not have any reasonable expectation of success, since there would be no reason to arrive at the method of claim 26.

Also as stated above, the necessary modification required to adapt Piesold to the present methods would destroy the intent, purpose and function of the device in Piesold and thus this reference doess not properly support a *prima facie* case of obviousness.

Dependent claims 27 to 29 depend directly or indirectly from independent claim 26 and thus include all of the features of claim 26. Thus, for the same reasons as stated above for claim 1, Applicant submits that the combination of Chou, Bernhardt and Piesold references do not render claims 26 to 29 obvious.

In view of the foregoing, reversal of the rejection of independent claim 26 and claims 27-29 dependent thereon under 35 U.S.C. 103 in view of Chou, Bernhardt and Piesold is therefore requested.

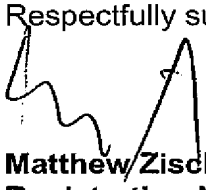
Summary

Applicant appreciates that the presently claimed methods employ a novel and inventive combination of straightforward size filtration, affinity interactions and detection techniques. However, the use of straightforward techniques can provide a novel and inventive method when combined in novel and inventive ways, as is the case with the presently pending claims.

Furthermore, Applicant points out that the Examiner has needed to combine four or three references in an attempt to make a *prima facie* case of obviousness, and still has not been successful with either combination. Applicant submits that the need on the Examiner's part to combine such a large number of references and still failing to find all of the elements of the claims, underscores the fact that the presently claimed methods are not obvious.

For the foregoing reasons, it is submitted that the Examiner's rejections under 35 U.S.C. 103 of claims 1-5, 7, 8 and 22-29 are not well founded, and reversal of the rejections is respectfully requested.

Respectfully submitted,



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Claims Appendix

1. (previously presented) A method for detecting the presence of an analyte particle in a fluid, said method comprising, sequentially:

   filtering a sample of said fluid from a first chamber to a second chamber through a filter sized to pass said analyte particle and particles smaller than said analyte particle, retaining in said first chamber particles in said sample larger than said analyte particle thereby forming in said second chamber a filtered sample;

   adding to said filtered sample in said second chamber a reagent that specifically interacts with said analyte particle to form a reagent-analyte particle complex that is larger than said analyte particle;

   filtering said filtered sample from said second chamber through a filter sized to pass particles that are smaller than said reagent-analyte particle complex thereby forming in said second chamber a further filtered sample;

   testing said further filtered sample in said second chamber for the presence of residual particles, wherein the presence of said residual particles identifies the presence of said reagent-analyte particle complex in said second chamber, and wherein the presence of said-analyte particle complex is indicative of the presence of said analyte particle in said fluid and wherein the absence of said reagent-analyte particle complex in said second chamber is indicative of the absence of said analyte particle in said fluid.

2. (original) A method in accordance with claim 1, wherein said fluid is a biological fluid.

3. (original) A method in accordance with claim 2, wherein said biological fluid is blood.

4. (original) A method in accordance with claim 3, wherein said analyte particle is human immunodeficiency virus.

5. (original) A method in accordance with claim 1, wherein said analyte particle is a virus.

6. (canceled)

7. (previously presented) A method in accordance with claim 4, wherein said reagent is truncated CD4 glycoprotein.

8. (original) The method of claim 7, wherein said filtering is performed using micro-injected molded plastic.

9. to 21. (canceled)

22. (previously presented) A method for detecting the presence of human immunodeficiency virus in a fluid, said method comprising sequentially:
filtering a sample of said fluid from a first chamber to a second chamber through a filter sized to pass said human immunodeficiency virus and particles smaller than said human immunodeficiency virus, retaining in said first chamber particles in said sample larger than said human immunodeficiency virus thereby forming in said second chamber a filtered sample;

adding to said filtered sample in said second chamber a reagent that specifically interacts with said human immunodeficiency virus to form a reagent-human immunodeficiency virus complex that is larger than human immunodeficiency virus;

filtering said filtered sample from said second chamber through a filter sized to pass particles that are smaller than said reagent-human immunodeficiency virus complex thereby forming in said second chamber a further filtered sample;

testing said further filtered sample in said second chamber for the presence of residual particles, wherein the presence of said residual particles identifies the

presence of said reagent-human immunodeficiency virus complex in said second chamber, and wherein the presence of said reagent-human immunodeficiency virus complex is indicative of the presence of said human immunodeficiency virus in said fluid and wherein the absence of said reagent-human immunodeficiency virus complex in said second chamber is indicative of the absence of said human immunodeficiency virus in said fluid.

23. (previously presented) A method in accordance with claim 22, wherein said reagent is truncated CD4 glycoprotein.

24. (previously presented) A method in accordance with claim 23, wherein said fluid is a biological fluid.

25. (previously presented) A method in accordance with claim 24, wherein said biological fluid is blood.

26. (previously presented) A method for detecting the presence of human immunodeficiency virus in a fluid, said method comprising:

filtering a sample of said fluid to remove all particles in said sample larger than said human immunodeficiency virus to form a filtered fluid;

introducing said filtered fluid into a chamber;

adding to said filtered fluid a reagent that provides a specific binding site for any human immunodeficiency virus in said filtered fluid to form a reagent-human immunodeficiency virus complex that is larger than said human immunodeficiency virus in said chamber;

filtering said sample after said adding to remove particles from said chamber that are smaller than said reagent-human immunodeficiency virus complex to form a remaining sample in said chamber;

testing said remaining sample in said chamber for the presence of a residue of said reagent-human immunodeficiency virus complex, wherein the presence of said residue in said chamber identifies the presence of said human immunodeficiency virus within said fluid and wherein the absence of said residue in said chamber identifies the absence of said human immunodeficiency virus within said fluid.

27. (previously presented) A method in accordance with claim 26, wherein said reagent is truncated CD4 glycoprotein.

28. (previously presented) A method in accordance with claim 27, wherein said fluid is a biological fluid.

29. (previously presented) A method in accordance with claim 28, wherein said biological fluid is blood.

Evidence Appendix

None

Related Proceedings Appendix

None